Applicants assert that the identified sequences represent a specific class of genes that is involved in late stages of stem cell differentiation and development. These genetic loci encode genetic functions that are not inhibitors of cell death or apoptosis and are not involved in the general survival, *i.e.*, house-keeping functions, of teratocarcinoma cells because one functional allele of these genes does not trigger cell death or apoptosis and that one functional allele of these genes is sufficient for cell survival and growth. The usefulness of such genes is well-established in the art. Support regarding gene function of the presently claimed oligonucleotides and polynucleotides can be derived logically as explained below.

The insertion of a gene trapping vector into a gene will interrupt the proper function of that copy of the gene. If the gene is an inhibitor of cell death or apoptosis and both copies are required for normal function, the cell will die and be lost in a population, and the gene will not be identified by the present invention. If the gene is required for cell viability, this reduction of gene activity by 50% will in most cases result in a decrease in cell viability. Thus, in a population of cells exposed to the gene trapping vectors of the invention, the percentage of cells that can be identified as suffering from a 50% reduction in gene activity of a gene required for cell viability is disproportionally lower than the percentage of cells that have a 50% reduction in gene activity of a gene not required for cell viability. On the other hand, in the same population, the percentage of cells with an insertion of the gene trap vector in a gene that is not required for cell viability will be higher than the percentage of cells that have a 50% reduction in gene activity of a gene in the genome that are required for cell viability. As the sequences of the invention are derived from the cells with insertions of the gene trap vector, the number of identified genes that are not required for cell viability will be higher compared to the number of identified genes that are required for cell viability. The gene-trapping method of the present invention therefore pre-selects a class of genes that is not involved in cell viability. Genes that are not involved in cell viability are likely to be involved in late stages of stem cell differentiation and development. Thus, the gene trap method enriches a class of genes that is involved in late stages of stem cell differentiation and development.

Further, the gene trap method identifies genes that would not have been identified by conventional forward genetics. By conventional forward genetics, the cells are mutated and selected for an observable phenotype. Subsequently, the mutation is genetically mapped by following the phenotype. Based on the genetic map position, the gene is cloned.

Without an observable phenotype, the mutation cannot be genetically mapped and the associated gene cannot be cloned. The gene trap method, in contrast, pre-selects for a class of genes that is not required for cell viability, and effectively narrows the scope of the identification process. In other words, the present invention allows one to identify genes that do not have an easily observable phenotype. Applicants submit that the claimed oligonucleotides and polynucleotides are specifically identified and biologically validated (i.e., by actually being spliced) exons that had not been previously identified by conventional molecular biology approaches. These oligonucleotides and polynucleotides represent transcripts of nominal abundance in conventional cDNA libraries.

Applicants respectfully point out that the Utility Guidelines provide that, in evaluating evidence related to utility, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed and whether the asserted utility appears to contravene established scientific principles and beliefs. For the claimed utility to be credible, the invention must be "believable based on the record or the nature of the invention" (M.P.E.P. 2107.02(III)(A).

Applicants assert that because of the nature of the invention and for the reasons set forth above, the sequences of the invention which are pre-selected for sequences representing genes that are involved in the differentiation and development of teratocarcinoma cells have credible utility.

The Examiner further contends that an invention which requires further research in order to have currently available utility fails to meet the utility requirements. In response, Applicants respectfully point out that the pre-selected class of genes have currently available utility in the identification of important regulators of cell differentiation. For example, the sequences identified by the gene trap method can be used to assemble a micro-array. When the micro-array is hybridized with RNA from teratocarcinoma cells of different differentiation stages, genes that are involved in the differentiation of this type of cells are identified. Using a micro-array with the class of genes that is pre-selected for genes involved in differentiation and development as opposed to cell viability reduces the number of genes that need to be screened compared to a micro-array of genes randomly picked from a genome sequence database.

The Examiner contends that claims 3 and 10-14 lack written description under 35 U.S.C. § 112, first paragraph due to a lack of sequence disclosure beyond SEQ ID NOS. 9-

18. Applicants assert that the skilled artisan can distinguish the claimed sequences from other sequences and can identify the species that the claims encompass. Thus, claims 3 and 10-14 meet the standard for the written description requirement under 35 U.S.C. § 112, first paragraph. Merely because the sequences may contain, for example in claim 12, sequences in addition to at least 130 contiguous nucleotides of any one of SEQ ID NOS:9-18 should not be rejected for lack of written description. Here, for example in claim 12, the new aspect of the claimed isolated polynucleotides is the stretch of at least 130 contiguous nucleotides of any one of SEQ ID NOS:9-18, which is unambiguously described in the application by virtue of the sequence listing. Applicants respectfully request that the rejections of claims 3, and 10-14 under 35 U.S.C.§112, first paragraph, be withdrawn.

CONCLUSION

Applicants submit that Claims 3, and 10-14 satisfy all of the criteria for patentability and are in condition for allowance. Accordingly, Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application.

Respectfully submitted,

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By: [signature]

Date: February 3, 2003

[signature] 30,742

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Enclosures